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The role of estrogen receptors in the auditory system

AKADEMISK AVHANDLING

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ABSTRACT

Both laboratory and clinical studies have previously demonstrated estrogenic effects on the auditory function. The overall scope of this study was to investigate the physiological and molecular involvement of estrogens and estrogen receptors alpha (ER α) and beta (ER β) in hearing physiology. ER α and ER β were localized in a number of central auditory structures in mice, and their differential localization suggested distinct roles in auditory processing. ER expression was assessed in young, prepubertal and aged mice with diverging levels of estrogens. Changes in the expression patterns were not uniform between groups, suggesting that region-specific mechanisms regulate ERs expression. Neither age group showed sex differences in ER expression. Chronic 17 β -estradiol treatment in ovariectomized mice resulted in molecular changes in the central (inferior colliculus) and peripheral (cochlea) auditory structures. Down-regulation of ER α mRNA in the cochlea and inferior colliculus may be a direct effect of estrogen-induced feedback inhibition of ER α transcription. No changes were noted for ER β mRNA levels, suggesting that ER β is constitutively expressed, rather than directly regulated by circulating hormones. Concurrent with these molecular changes, auditory-related behavioral parameters were altered by 17 β -estradiol treatment. Improved prepulse inhibition of the acoustic startle response after 17 β -estradiol treatment, suggested an estrogenic modulation of sensorimotor gating. Investigation of mice deficient in ER α (ERKO mice), ER β (BERKO mice) and aromatase (ARKO mice) suggested a protective role for ER β in the auditory system against acoustic trauma. Brain derived neurotrophic factor (BDNF), which is a neuroprotective peptide that can be induced by estrogens, increased in the cochlea after treatment with an ER β -selective agonist, whereas it was decreased in the cochlea of BERKO and ARKO mice. ER β -mediated neuroprotective mechanisms against noise exposure involving neurotrophic factor BDNF, were suggestive of estrogens' supportive contributions to the auditory function. Analysis of ER α , ER β and BDNF levels in the cochlea during the reproductive cycle, revealed regulation of ER α but not ER β or BDNF by endocrine activity. ER α levels were lower in high-estrogen conditions, suggesting that ER α expression in the peripheral auditory system is regulated by circulating sex hormones and acts as an interface between endocrine activity and the auditory system. Taken together, these results suggest an involvement of estrogens and their receptors along with neurotrophic factors in the physiology of the mammalian auditory system. Unraveling the distinct roles of estrogen receptors in the auditory system may provide novel treatment strategies and pharmacological targets for the support of hearing.

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